

**A REVIEW ON SEVERE SEPSIS AND SEPTIC SHOCK IN GERIATRIC POPULATION –
EPIDEMIOLOGY, RISK FACTORS, DIAGNOSIS, MANAGEMENT STRATEGIES AND
TREATMENT MODALITIES****Priyanka Tanwar^{1*}, Mamta Naagar² and Manish Kumar Maity²**¹Department of Pharmacology, Bhagvan Mahavir Institute of Medical Sciences, Sonipat-131030, Haryana, India.²Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana-133207, Ambala, Haryana, India.***Corresponding Author: Priyanka Tanwar**

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ABSTRACT

The elderly population is becoming more likely to suffer from severe sepsis and septic shock, which is increasing the number of patients admitted to intensive care units (ICUs). Sepsis is more common among the elderly because of co-occurring co-morbidities, extended hospital stays, lowered immunity, functional restrictions, and most importantly, the natural ageing process. Because the early clinical picture may be unclear and ageing increases the likelihood of a fast progression in sepsis to severe sepsis and septic shock, a lower threshold and a greater index of suspicion are needed to identify sepsis in this patient population. With certain adjustments, established worldwide norms serve as the foundation for management practices. Age itself is an independent risk factor for death in patients with severe sepsis, however, many patients respond well to timely and appropriate interventions. Because the prognosis is not dire, patient and family wishes should also be considered before restricting or postponing treatment for elderly patients with severe sepsis due to professional bias. In addition to focussing on a successful functional recovery, future researches on the therapy of sepsis should also ensure social independence and a high standard of living following ICU release.

KEYWORDS: Elderly patients, Intensive care units outcome, Severe sepsis.**INTRODUCTION**

Worldwide, the number of elderly people hospitalised to intensive care units (ICUs) has surged in recent times.^[1] This "demographic transition" process may be described by both a fall in death rates, which raises life expectancy, and a decrease in fertility, which lowers the birth rate. According to the statistical predictions, the old will increase faster than any other age group in the near future, and by 2050, there will be more geriatric people than young age group people.^[2] In the geriatric population, sepsis is a significant source of morbidity and death. Research on the diagnosis and treatment of sepsis typically excludes participants with several co-morbidities or those who are very old (older than 80 years); nevertheless, as the population ages and becomes sicker, this subset of the population will be admitted to intensive care units (ICUs) more frequently, and treating intensivists will face significant challenges in managing them. We have attempted to examine the care, risk factors, susceptibility, and prognosis of geriatric individuals with septic shock and severe sepsis through this study. Additionally, we have made an effort to pinpoint the areas that warrant further research in order

to potentially enhance results for this specific patient group.

Epidemiology

Severe sepsis and septic shock are the most severe types of sepsis, which is described as an inflammatory bodily reaction to infection.^[3] Sepsis is the second most common cause of mortality for patients in non-coronary intensive care units (ICUs) despite improvements in the care of septic patients.^[4] Sepsis is more common and its incidence rises with age.^[5] According to Angus et al.'s^[5] analysis of discharge records from seven US hospitals for the year 1995, there were 3.0 incidences of severe sepsis for every 1000 people. On the other hand, 26.2 incidences of severe sepsis per 1000 people were seen among elderly individuals. In this study, the mean age of patients with severe sepsis was 63.8 years; in the subsequent study, it rose to 68.2 years.^[4,5] Despite making up just 15% of the US population, two thirds of sepsis patients admitted to hospitals are geriatric.^[4] Severe sepsis is becoming more common as a whole as well.^[6,7] Between 1993 and 2003, the number of patients hospitalised with severe sepsis increased by 1.7 times,

according to Dombrovskiy et al's study.^[6] According to a different research conducted by Martin et al, older patients had a 20% higher incidence of sepsis than younger ones.^[4] Studies from the eastern half of the world have found similar findings of an increasing frequency of sepsis, with the mean age of patients with severe sepsis being about 60 years.^[8,9] Serious sepsis-related death rates rise with age as well, with the oldest patients (those over 85 years of age) having the greatest fatality rates.^[9 - 12] Data on the prognosis of geriatric people with sepsis and septic shock are few. A small number of research carried out in this particular patient group have demonstrated that older individuals are more likely than their younger counterparts to experience severe sepsis and septic shock.^[4,6,9]

Risk factors

The elderly are more likely to get sepsis due to a number of risk factors.

- 1. Preexisting co-morbidities and drugs for these chronic illnesses** - Chronic co-morbidities such as cancer, diabetes, obesity, and HIV, among others, may contribute to the heightened risk of sepsis in the elderly.^[6] These are all far more important for geriatric patients. Sepsis susceptibility is frequently elevated in patients with concomitant conditions such as renal or lung disease.^[4,13,14] Co-morbidities by themselves are insufficient to weaken immunity; other variables including medication, equipment, and frequent hospital stays also contribute to this.^[15]
- 2. Pre-admission functional status** - It has been discovered that pre-admission functional state is an independent predictor of prognosis in older patients, and is far more significant than concomitant illness.^[16,17] Poor functional status can be caused by a variety of factors, such as^[17,18]: (1) Changes in trophic hormone responsiveness (growth hormones, androgens, and oestrogens); (2) Sarcopenia due to accelerated muscle loss; (3) Neurological alterations; (4) Altered cytokine regulation; (5) Changes in protein metabolism; and (7) Changes in dietary intake.
- 3. Malnutrition** - The elderly are also susceptible to malnutrition, which has been linked to a number of conditions and behaviours, including inactivity, a lack of funds or resources, problems with mobility and transportation, social isolation, functional limitations, poor or restricted diets, chronic illnesses, dementia, depression, poor dentition, polypharmacy, and alcohol or drug abuse.^[18]
- 4. Endocrine deficiency** - Elderly individuals are also more susceptible to infection due to concomitant endocrine abnormalities such as hypogonadism, hypothyroidism, and hypoadrenalism, which affect how the body responds to sepsis.

5. Aging - Age itself has been identified in many studies as an independent risk factor for the propensity to develop severe sepsis.^[4,19,20]

6. Other risk factors - Elderly people are also more likely to become colonised by gram-negative bacteria, which can be resistant to many drugs and put them at risk for sepsis.^[19] This increased colonisation may be caused by living in a nursing home, being often hospitalised and undergoing procedures like urine catheterizations, having a low functional status or abusing several drugs.

Immune system in the geriatric age group patients

Older adults have aberrant immune systems that are in a condition of immunosenescence.^[21] This immunosenescence has a complicated, multifaceted aetiology. As people age, their humoral immune responses and cell-mediated immunity both experience functional deficits.^[21] A key organ in adaptive cell-mediated immunity, the thymus shrinks with ageing and stops functioning entirely by the age of 60, which causes the T-cell repertoire to change from naive to memory T-cells.^[21,22] These memory cells respond to antigens by expressing fewer co-stimulatory molecules such as CD40 ligand and CD28, having a restricted potential for proliferation, and reducing the activation of mitogen-activated protein kinase.^[22] Ageing also causes a progressive decline in the numbers of B cells and plasma cells.^[23] However, age causes a rise in polyspecific, low affinity T-cell independent immunoglobulin levels.^[23] Certain immunoglobulins have autoantibody characteristics.^[24] The elderly are less able to develop specific opsonophagocytic antibodies against neoantigens, even while they still maintain antibodies against previously exposed antigens.^[21] The ageing process has an impact on innate immunity in various ways, and it is not immune to these effects. Significant functional changes occur in macrophages, including decreased bactericidal activity, decreased antigen processing and expression to T cells, and altered expression and function of toll-like receptors.^[25] In addition to macrophages, other innate immunity-related cells such as neutrophils and natural killer cells also have deficiencies, which results in a decrease in the elderly's ability to identify and eliminate contaminated cells.^[26]

Impact of ageing on pathophysiology of severe sepsis

Apart from the immunosenescence condition that makes older people more likely to have sepsis, changes in the body's reaction to sepsis also result in a more severe presentation of infection. A crucial part of the pathophysiology of sepsis is the activation of the coagulation cascade by severe sepsis.^[21] The higher risk of thrombosis and thromboembolism observed in the elderly can be explained by an aging-related rise in plasma levels of fibrinogen, factor VII, factor VIII, factor IX, and other clotting factors that is further amplified during sepsis.^[21] Geriatric people also produce more plasminogen activator inhibitor type 1 at a higher rate,

which may be a factor in the senior patient's poor fibrin clearance from the circulation.^[21] A portion of the greater short survival rates with drotrecogin α (activated) in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) experiment can be explained by the combined effects of ageing and sepsis on the coagulation cascade.^[12,27] Geriatric people also have an aberrant cytokine response.^[21] Type 2 cytokines (IL-4, IL-10) are produced instead of type 1 cytokines (interleukin (IL)-2, tumour necrosis factor (TNF)- α).^[28] On the other hand, the generation of IL-1, IL-3, TNF, interferon- γ , IL-8, and IL-12 is often either unchanged or elevated in the elderly.^[21] Compared to younger patients, this puts the elderly at risk for systemic infection by microbial pathogens and typically longer proinflammatory responses. This also illustrates the aberrant way that counter-regulatory cytokines, such as IL-10, remove microbial infections.^[21] The notion of cardiac depression linked to sepsis is attributed to several variables, such as nitric oxide, TNF, and maybe other inflammatory cytokines including IL-1 and IL-6, which have an adverse inotropic effect.^[29] Geriatric septic patients may have a worse prognosis as a result of this being made worse by aging.^[30,31] In comparison to younger participants, the elderly also exhibit a more severe reaction to endotoxins, including deeper hypotension, an excess of adrenaline, a delayed recovery of blood pressure, and a more significant cytokine response.^[32]

Diagnosis of sepsis in the geriatric patients

It is difficult and likely that an infection in an aged person will go unnoticed if it is not clinically diagnosed. Sepsis in older individuals may manifest differently and with more severity than in younger ones.^[10] Geriatric patients may have a delayed or missing early inflammatory response to infection, which often results in symptoms and indications of sepsis. However, subsequent presentations may be quite severe, rapidly progressing to septic shock.^[13,21,26] Research indicates that in as many as 47% of senior septic patients, the febrile response may be attenuated.^[33] Unspecific indicators of sepsis, such as altered mental state, delirium, weakness, anorexia, malaise, falls, and incontinence all are frequently observed in the aged population.^[13] Diagnosing non-infectious illnesses in the elderly might be challenging due to similar results.^[13] Furthermore, a clear history may not be accessible in many individuals due to age-related dementia. Therefore, in this group, sepsis diagnosis requires a lower threshold and a greater index of suspicion.^[13,34] In addition to the aberrant reaction to infection, older patients might be difficult to get sufficient diagnostic specimens from due to a lack of cooperation in the weak, exhausted, incapacitated, and cognitively impaired.^[13,34] When doing high-quality imaging tests, positioning these individuals owing to osteoarthritis or other orthopaedic issues may prove difficult, this might limit the investigations' diagnostic value.^[34] The respiratory tract is the most frequent cause of sepsis in older people, followed by genitourinary infections.^[4] It is likely that

infections with organisms resistant to many drugs are more common in the aged population. An elevated rate of identification of isolates such as vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* among the elderly was noted in a survey of patients treated at haematology and cancer centres in the United States and Canada. According to research, individuals under 14 and older than 65 years old had the highest prevalence of extended-spectrum β -lactamase-producing *Klebsiella* species.^[35] Greater exposure to the healthcare system and cumulative antibiotic exposure are the explanations for the disproportionately higher prevalence of multi-resistant organisms in the elderly, albeit there are currently insufficient researches in this field to corroborate these findings.

Management of severe Sepsis and Septic Shock in the geriatric patients

The International Surviving Sepsis Guidelines^[36] should be followed for treating elderly patients with severe sepsis and septic shock. Early use of the sepsis resuscitation and treatment bundles has been demonstrated to enhance survival across a range of age groups with excellent compliance.^[37,38] It is recommended to adhere to the same management guidelines as young adults, which include early source control, early goal-directed therapy, and the use of low tidal volume during mechanical ventilation. Nonetheless, there are several particular factors that need to be taken into account while treating severe sepsis and septic shock in the elderly.

- 1. Resuscitation** - The cornerstone of the resuscitation bundle for treating severe sepsis and septic shock in both young people and elderly patients continues to be early goal-directed therapy.^[39] Research has demonstrated the efficacy of early goal-directed therapy in adults when combined with additional sepsis bundle strategies for the treatment of older patients^[40] Since the elderly's heart rate response to sepsis is muted, many strategies to increase cardiac output in them should instead concentrate on systolic function.^[41] According to Starling's law, left ventricular preload affects the heart's systolic output. As a result, anytime an elderly patient has to enhance his cardiac output, like during sepsis, it is imperative to maintain an appropriate preload.^[26] On the other hand, individuals with diastolic dysfunction linked to ageing may experience issues with excessive fluid administration.^[41] Due to relative resistance in the elderly and the potential for arrhythmia, particularly in individuals with a history of coronary artery disease, other treatments to increase tissue perfusion, such as dobutamine, may also have varying effects.^[42] The threshold to transfuse packed red blood cells should be maintained at haemoglobin of less than 7 g/dL and a target haemoglobin of 7-9 g/dL.^[43] Blood transfusion triggers should be the same as in young adults. The early goal-directed resuscitation protocol (first 6 hours of resuscitation) aims for a haematocrit

of 30% in patients with low central venous oxygen saturation and in patients with active coronary artery disease, which may be common in the elderly patients.^[40,44] The threshold of 7 g/dL, however, is in conflict with this protocol. In spite of sufficient fluid challenges, vasopressors such as dopamine or norepinephrine can be employed to maintain perfusion in the event of life-threatening hypotension.^[36]

- 2. Source Control and Antibiotics** - Antimicrobial dosage should be determined by age-related variations in pharmacokinetic and pharmacodynamic parameters, such as decreased lean body mass and increased body fat, shock-induced reduction in hepatic blood flow, and declines in renal function, including glomerular filtration rate, tubular secretion, and renal blood flow.^[45, 46] Elderly people are also more likely to have negative effects from antibiotics.^[46,47] To prevent any side effects, the first bolus dosage and general vigorous dosing to obtain maximal therapeutic dose should not be compromised.^[46] Two essential elements of the management bundle of surviving sepsis recommendations are source control of infection and early administration of adequate antibiotics.^[36,37] The infection source should be located as soon as possible, and suitable source control measures, such as the removal of contaminated foreign objects (intravascular catheters), the drainage of abscesses or other infected fluid collections, or the early consideration of definitive management of anatomical deformities supporting microbial contamination, should be considered.^[26,36] All ages are affected by the idea that insufficient early antibiotic treatment is independently linked to poor outcomes.^[47,48] Even in elderly sepsis patients, early antimicrobial medication initiation has been shown to dramatically reduce mortality.^[47-51] When sepsis is diagnosed, broad spectrum empirical antibiotic therapy should be started as soon as possible.^[36] This is after blood tests and samples from other potential infection sites have been collected for culture. The site, severity, and comorbidities of the patient; environmental factors, such as living in a nursing home or having a history of recurrent hospitalisations; and local factors, such as the expected microbiological organism and antimicrobial susceptibility patterns, should all be taken into account when developing empirical antimicrobial regimens.^[45,46] When applicable, shorter therapy courses, culturally-based de-escalation techniques, and clinical response techniques should also be employed.^[46]
- 3. Corticosteroids** - Elderly septic shock patients frequently have adrenal insufficiency.^[52] Nevertheless, these individuals seldom exhibit the laboratory results of hyponatraemia, hyperkalaemia, and eosinophilia, which may point to the existence

of adrenal insufficiency.^[52,53] Due to worries about the efficacy of steroids in general as well as their major side effects, such as hyperglycemia, immunosuppression (at high doses), poor wound healing, and worsening of myoneuropathy as a result of critical illness, the use of steroids for septic shock has remained controversial.^[54,55] Salgado *et al.*'s research^[53] added to the debate by demonstrating that ageing may not always be a risk factor for relative adrenal insufficiency. Because there is currently insufficient evidence, we advise against using low dose intravenous hydrocortisone in elderly patients experiencing septic shock except in specific clinical circumstances where the patient's blood pressure does not respond well to fluid resuscitation and vasopressor therapy, as advised by the surviving sepsis guidelines.^[36]

- 4. Activated protein C (Drotrecogin α)** - Recombinant human activated protein C (rhAPC)-treated individuals had a 6% absolute risk reduction (19.4% relative risk reduction) in 28-day mortality compared to placebo-treated patients, according to the PROWESS experiment conducted in 2001.^[27] 48.6% and 24.1%, respectively, of the 850 patients who were randomly assigned to receive rhAPC in this trial were older than 65.^[27] Subgroup analysis revealed that, among patients older than 75 years (386 patients), the treatment group had a 15.6% lower risk of hospital mortality and a 15.5% lower absolute risk of death at 28 days when compared to the placebo group, with no appreciable increase in bleeding risk.^[12] Among the senior patient subgroup, even long-term survival was considerably greater in the therapy group ($P = 0.02$).^[12] Therefore, if there are no contraindications, treating elderly patients with rhAPC who have septic shock and are at a high risk of dying from severe sepsis may be done safely.^[13,36] The same criteria that apply to younger patients still apply to those receiving rhAPC: Acute Physiology and Chronic Health Evaluation II > 25 and patients with sepsis-induced organ dysfunction of more than two organ systems, necessitating vasopressors despite fluid resuscitation.^[37]
- 5. Respiratory Failure and Mechanical ventilation** - Mechanical ventilation is frequently necessary for patients who have septic shock and severe sepsis. There exists an independent correlation between higher mortality and the demand for mechanical ventilation in older adults.^[10,56,57] When compared to the conventional tidal volume (12 mL/kg) group, the low tidal volume (6 mL/kg) group showed a 22% relative risk reduction in mortality, according to a study conducted by the Acute Respiratory Distress Syndrome (ARDS) Network.^[58] When low tidal volume ventilation was used in a subgroup study of 173 patients who were over 70, the absolute risk of death at 28 days was reduced by 9.9%.^[59] Therefore, even in senior patients with acute lung injury

(ALI)/ARDS, a tidal volume of 6 mL/kg (predicted) body weight is advised.^[60] Furthermore, patients with ALI/ARDS should have their plateau pressures assessed, with a lower limit objective of less than 30 cm H₂O initially set for plateau pressures. There is a lack of information on weaning in the senior population following ARDS; nevertheless, typical guidelines for younger persons, such as employing spontaneous breathing trials and standardised protocols to assess patients for weaning, can be applied to the elderly.^[60,61]

6. **Glycemic control** - In a cohort of mostly surgical ICU patients, van den Berghe et al,^[62] showed a substantial decrease in morbidity and mortality with intensive blood glucose (BG) management at 80 and 110 mg/dL. But in medical ICU patients, the same researchers were unable to show decreased mortality with the same methodology, and in the intensive BG control group, the risk of hypoglycemia (BG < 40 mg/dL) was six times higher (18.7% vs. 3.1%).^[63] Any advantage from stringent glycaemic control is perhaps negated by the major adverse events of hypoglycemia, since the increased rates of severe hypoglycemia linked with intensive insulin therapy were also observed in other studies and a meta-analysis.^[63 - 67] After stabilisation in the ICU, patients with severe sepsis should have a continuous intravenous infusion of insulin and glucose to maintain a blood glucose level of less than 150 mg/dL, according to the recommendations for surviving sepsis.^[36] Because older septic patients are more likely to have hypoglycemia, the 150 mg/dL goal seems safe in these individuals.
7. **Other issues** - The use of sedation and analgesia, prophylaxis for deep vein thrombosis, and stress ulcer prophylaxis which should be followed as for the younger adults are some further concerns regarding the management of older patients with severe sepsis.^[37] To shorten the time that patients need mechanical breathing, protocolised sedation regimens with daily sedation interruptions should be used.^[68] This might involve sedative medications that are infused continuously as opposed to being given as an intermittent bolus.^[68] Prophylactic devices or low-dose unfractionated heparin or low-molecular-weight heparin are recommended for the prophylaxis of deep vein thrombosis, whereas H₂-receptor blockers or proton pump inhibitors are recommended for the prevention of stress ulcers.^[36]
8. **End of life issues** - In addition to aggressively treating patients with severe sepsis and septic shock, doctors should be ready and able to offer elderly patients with a poor prognosis high-quality end-of-life care. The likelihood of having to decide whether to withhold or stop life-sustaining therapies rises with patient age; nevertheless, these choices should be tailored to the patient's and their family's

preferences rather than being based on the treatment's perceived futility.^[69 - 71] This entails prior care planning, which includes clearly informing the patient or their family of the expected results and reasonable treatment goals. The ultimate choice to discontinue or reduce therapy may be carried out in accordance with regional policies. The hospital ethics committee or teams analogous to it may offer support in making decisions on possibly ineffective or pointless life-sustaining therapies in challenging or complex circumstances.^[72]

Prognosis and Outcomes of severe sepsis in the geriatric patients

Elderly patients suffering from septic shock and severe sepsis have substantial death rates, ranging from 50% to 60%.^[4,9,73] Compared to younger cohorts, the death rate from severe sepsis in elderly patients is 1.3–1.5 times higher.^[4,9] Age has been shown to be an independent predictor of death in a number of studies.^[4,5,8,9] Compared to young individuals, older patients with sepsis had a higher mortality rate during hospitalisation and a higher need for professional nursing or rehabilitative cares.^[4] Many characteristics, including pre-infectious immune or genetic status, nosocomial occurrences, co-morbidities, severity of illness, age > 75 years, and impaired state of awareness, have been found to be independent predictors of outcome in critically sick patients.^[16,73] The presence of shock, high blood lactate levels, and organ failure, particularly respiratory and cardiac failure are poor prognostic markers in elderly individuals with severe sepsis.^[73] Health care strategies should take into account the patient's quality of life following the remission of sepsis. There is a paucity of information about survival and quality of life following a severe sepsis episode, particularly in the elderly. Elderly patients are more likely to experience worse functional outcomes during their ICU stay, including the development of new functional restrictions in addition to their inability to resume normal living activities.^[74] Rather than the severity of the disease at admission, the elderly's long-term prognosis is mostly based on their functional status.^[75] According to a research by Ely et al.^[12] discharges from hospitals to nursing homes or alternative health care facilities (55%) had a higher likelihood of going to the elderly (≥ 75 years of age) than to their homes (45%). A further research discovered that being older than 80 years was an independent predictor of being discharged from hospital.^[76] Therefore, future studies on the treatment of severe sepsis should focus on both better functional outcomes for these patients as well as increased survival.

Healthcare Costs and Rationing of resources

The treatment of sepsis has significant budgetary effects on the few healthcare resources. According to data, the yearly cost of managing sepsis was \$17 billion in the year 2000 alone.^[5] Furthermore, the care of patients over 65 accounted for over half of this expense, while the care of patients over 75 accounted for around one-third.

Along with an ageing population and rising mortality, sepsis frequency is expected to rise by more than 5% annually.^[4] As a result, treating sepsis in the elderly will be extremely expensive.^[2,5] This has sparked a heated discussion over resource allocation, intensive care unit admittance standards, and whether or not to continue treating elderly people. There are few people who favour refusing old people access to the intensive care unit (ICU) or providing them with subpar care based just on their age.^[77–82] There is sufficient data to conclude that, even in the case of the elderly, higher treatment intensity is associated with better survival and favourable long-term outcomes.^[80,82] Therefore, a senior patient's age alone shouldn't be a factor in determining whether or not they are admitted or treated appropriately for sepsis.

Future perspectives

Data on severe sepsis in the elderly are few, particularly when it comes to variables that affect prognosis, quality of life, and functional success following sepsis therapy. The extremely old are typically excluded from antisepsis and antimicrobial agent studies due to the prevailing belief that they have a lower propensity to react to therapy. However, future trials should also target this patient age range in order to develop the best healthcare strategies as the population ages and the number of sepsis cases rises. The effectiveness of preventative interventions and the use of bundled techniques in the treatment of severe sepsis in the elderly should also be the focus of future research.

DISCUSSION AND CONCLUSION

Because of the higher medical, social, and financial resources required, as well as the accompanying clinical co-morbidities, managing older patients in the ICU is never easy. Not only are severe sepsis and septic shock more prevalent, but they are also linked to increased morbidity and fatality rates in older individuals. Sepsis in this age group requires a greater index of suspicion and a lower threshold for diagnosis. Prompt, proactive, and well-rounded care may help these patients achieve better results. Nonetheless, future clinical trials with older patients will aid in determining the best course of treatment.

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